BMJ Open

Triple-negative breast cancer prevalence in Africa: a systematic review and meta-analysis

Shawn M Hercules [1,2,3] Meena Alnajar [1,4] Chen Chen [1,5] Stefan M Mladjenovic [1,6,7] Bolade Ajarat Shipeolu [1,8] Olga Perkovic [9] Greg R Pond,[10] Lawrence Mbuagbaw [11,12,13,14,15,16] Kim RM Blenman [17,18] Juliet M Daniel [1,2]

To cite: Hercules SM, Alnajar M, Chen C, *et al*. Triple-negative breast cancer prevalence in Africa: a systematic review and meta-analysis. *BMJ Open* 2022;**12**:e055735. doi:10.1136/bmjopen-2021-055735

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-055735).

Received 22 July 2021
Accepted 08 May 2022

For numbered affiliations see end of article.

Correspondence to
Dr Juliet M Daniel;
danielj@mcmaster.ca

ABSTRACT

Objective The aggressive triple-negative breast cancer (TNBC) subtype disproportionately affects women of African ancestry across the diaspora, but its frequency across Africa has not been widely studied. This study seeks to estimate the frequency of TNBC among African populations.

Design Systematic review and meta-analysis using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

Data sources PubMed, EMBASE, African Journals Online and Web of Science were searched on 25 April 2021.

Eligibility criteria for selecting studies We included studies that use breast cancer tissue samples from indigenous African women with sample size of eligible participants ≥40 and full receptor status for all three receptors (oestrogen receptor (ER)/progesterone receptor (PR)/human epidermal growth factor receptor 2 (HER2)) reported.

Data extraction and synthesis Two independent reviewers extracted data and assessed risk of bias using the modified assessment tool by Hoy *et al.* (2012) for prevalence studies. A random-effects meta-analysis was performed, and data were pooled using the inverse-variance method and logit transformation. Pooled frequencies were reported with 95% CIs calculated with the Clopper-Pearson method and heterogeneity quantified with I^2 statistic. GRADE assessed the certainty of the evidence.

Results 1808 potentially eligible studies were identified of which 67 were included in the systematic review and 60 were included in the meta- analysis. Pooled TNBC frequency across African countries represented was estimated to be 27.0%; 95% CI: 24.0% to 30.2%, I^2=94%. Pooled TNBC frequency was highest across West Africa, 45.7% (n=15, 95% CI: 38.8% to 52.8%, I^2=91%) and lowest in Central Africa, 14.9% (n=1, 95% CI: 8.9 % to 24.1%). Estimates for TNBC were higher for studies that used Allred guidelines for ER/PR status compared with American Society of Clinical Oncology(ASCO)/College of American Pathologists(CAP) guidelines, and for studies that used older versions of ASCO/CAP guidelines for assessing HER2 status. Certainty of evidence was assessed to be very low using GRADE approach.

Conclusion TNBC frequency was variable with the highest frequency reported in West Africa. Greater emphasis should be placed on establishing protocols for assessing receptor status due to the variability among studies.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Previous studies have reported higher oestrogen receptor-negativity among West African countries compared to East African countries, but no review or meta-analysis has been solely focused on the frequency of triple-negative breast cancer (TNBC) across the African continent.
⇒ Certainty of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach.
⇒ Evidence of high frequency of TNBC and poor prognostic clinical factors highlights the need for early breast cancer detection across the continent.
⇒ There was evidence of variable methods used to assess receptor status across the African continent.
⇒ Only 20 out of 54 African countries were included in this study where there was a lack of cancer registry and population-based data, which suggests that our estimate for TNBC frequency across the continent is not fully accurate; however, given the available data, this is the best estimate from included studies.

INTRODUCTION

Breast cancer (BCa) mortality rates have markedly increased across Africa where estimated age-standardised rates in 2020 ranged from 20 deaths per 100,000 women across Northern Africa to 27 deaths per 100 000 women in Western Africa.[1–3] BCa has thus been dubbed an emerging epidemic in Africa.[4] Indeed, a recent systematic review and meta-analysis found that female BCa incidence rates increased from 23.1 to 26.3 per 100,000 between 2000 and 2015 across the continent.[5] Women of African ancestry (WAA) across the globe and indigenous African women are more likely to receive a poorer BCa prognosis compared with women of other ancestries.[6] Multiple studies

often posit poorer prognosis as a result of healthcare systems across Africa, where there is limited capacity and health infrastructure, for example, inadequate screening and diagnostic services.[7] However, BCa prevalence by subtype, as defined by receptor status, is strikingly different for indigenous African women compared with the BCa prevalence profile of Western countries and is not simply explained by limited access to healthcare.[6]

Immunohistochemistry (IHC) is routinely used to classify BCa into molecular subtypes according to the presence or absence of the oestrogen (ER) and progesterone (PR) receptors and the human epidermal growth factor receptor 2 (HER2). Triple-negative breast cancer (TNBC) is characterised by the lack of expression of all three biomarkers (ER, PR and HER2), which makes TNBC untreatable with targeted therapies such as tamoxifen and herceptin.[8 9] This BCa subtype is often associated with earlier disease-onset, advanced-stage tumours and aggressive disease progression when compared with other BCa subtypes.[10 11] Additionally, TNBC has been shown to disproportionately affect African women, and younger WAA and Hispanic women in North America,[11] where the prevalence of TNBC in WAA has been estimated to be more than twice the prevalence in non-Hispanic white women.[12] There is also a higher mortality rate from TNBC and more advanced stage at diagnosis in WAA.[13] Thus, it is important to investigate what seems to be an ancestral predisposition to TNBC since the reasons for this disparity in TNBC prevalence and outcomes are not fully understood. Studies to date have not compiled adequate information on TNBC frequency or considered reported frequency and routine practices associated with diagnosis and treatment across the African continent.

This systematic review and meta-analysis aims to increase understanding and knowledge regarding the frequency of TNBC across the African continent. The paucity of data and information on TNBC in Africa underscores the importance and urgency of such a review. A previous review reported higher ER-negativity among West African countries compared with East African countries[6] and a previous meta-analysis investigated ER-positivity across Africa[14] but no review or meta-analysis has been solely focused on the frequency of TNBC cases across the African continent. This review complements current biomedical research on TNBC and provides context for areas where TNBC research continues to expand. Improved understanding of TNBC frequency in continental Africa can further inform strategies for BCa detection and management for WAA globally. Due to shared ancestry between North American WAA and indigenous West African women,[15] we hypothesise that there will be higher TNBC prevalence rates in countries across West Africa compared with other regions (North, East, Central, Southern) across Africa.

METHODS

Search strategy and selection criteria

We used Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines as a framework for our systematic review and meta-analysis[16] as well as Meta-analysis of Observational Studies in Epidemiology guidelines.[17] On 25 April 2021, we searched PubMed, EMBASE, African Journals Online and Web of Science for relevant articles without date or language restrictions. Start date of the search was from inception of each database. A detailed version of our search strategy used in PubMed was modified for other databases. Search strategy and these modifications can be found in online supplemental table S1. Briefly, all search terms were Medical Subject Heading terms, including TNBC terms ('TNBC', 'triple-negative*', 'triple negative') and terms for African countries ('Africa', 'African' and names of all 54 African countries) and outcome variables ('rate*', 'prevalence', 'epidemiology'). We included all studies that met the inclusion criteria. The inclusion criteria were as follows: studies that use BCa tissue samples from indigenous African women of any age, in any care setting and at any geographic location; sample size of eligible participants was ≥40 (as slightly more stringent criteria since normal distribution could be assumed at n=30[18]); studies that demonstrate at least one of the following: report on receptor status of breast tumours including ER, PR and HER2; any primary study from which TNBC frequency could be estimated among BCa cases, including but not limited to observational studies, cross-sectional studies and case–control studies where controls were not included in TNBC frequency calculations.

We excluded editorials, single case reports, case series and commentaries; studies that assessed diagnostic measures and treatment options for women with TNBC in the absence of assessment of its frequency; studies conducted in non-African nations without assessment of indigenous African TNBC rates or that of first-generation African immigrants. Study selection began by screening titles and abstracts of articles collected after employing the search strategy. The full text of these articles was then reviewed to assess inclusion. Two data abstractors independently reviewed articles at both the title/abstract and full-text review stages. When there were discrepancies, a consensus was made in consultation with a third reviewer. The protocol for this review was not registered. Non-English studies were included after translation through Google Translate followed by verification of translation by a French speaker.

Quality assessment

Studies which passed full-text review (online supplemental table S2) were evaluated for risk of bias using a tool developed by Hoy and colleagues specifically intended for prevalence studies.[19] Each study was assessed according to 10 items assessing internal validity (online supplemental table S3) and assigned to have either low (score of 1) or high (score of 0) risk of bias for each

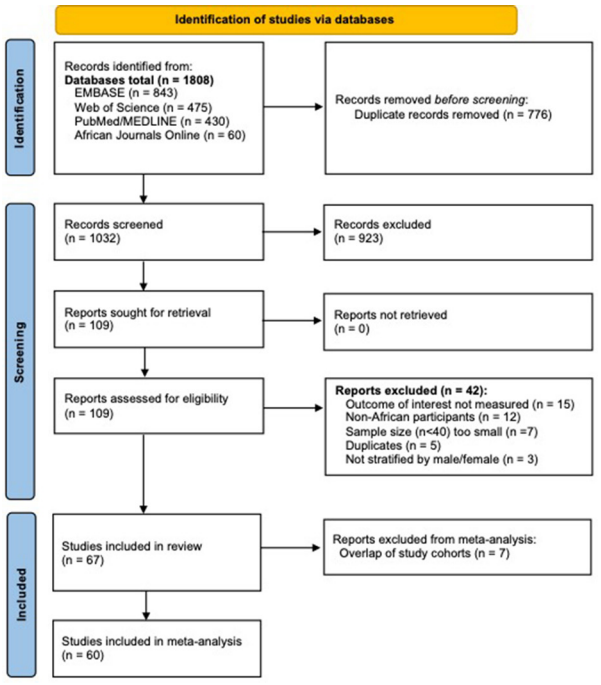

Figure 1 PRISMA flowchart accounting for all articles included in the narrative synthesis and meta-analysis. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

question by two independent reviewers. A third reviewer mediated discrepancy and a final score per question was agreed on. Studies were then classified based on the total score for all questions in the quality assessment tool as having a high (≤5), moderate (6–8) or low (≥9) risk of bias.

Assessing the certainty of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework[20] was used to assess the overall certainty of available evidence on the frequency of TNBC across the African continent. This framework considered factors such as study design, risk of bias, inconsistency, indirectness, imprecision and publication bias.

Data analysis

After reviewing full-text articles, a heat map was constructed with the number of studies, TNBC frequency and number of participants per country across African populations for unique studies using Google Sheets. All meta-analyses, meta-regressions and sensitivity analyses were completed using R (V.4.0.2).[21] Using the *metaprop* package in R, we conducted a meta-analysis of TNBC frequency among indigenous African women with BCa, stratified by country, region, risk of bias assessment, year of publication and the use of a validated tool for assessing receptor status. Logit transformation was used to stabilise the variances and a random effects model with inverse-variance method for pooling frequencies and Clopper-Pearson method for calculating CIs were used for our meta-analyses. Pooled TNBC frequency was estimated separately per country and per region as two studies included data from more than one region. When studies investigated African and non-African participants, only data from African participants were included in meta-analyses. Heterogeneity between studies was assessed with Cochrane's Q, I^2 and H statistics. Meta-regression was done to explore heterogeneity using *metareg* package. We used Egger's test to investigate publication bias and small study effects using the *metabias* package.

RESULTS

Of the 1808 records identified, 1032 remained after removing duplicates from the various databases. After screening titles and abstracts, 932 records were excluded due to irrelevance. The full text for the remaining 109 records were screened and an additional 42 studies were excluded because they did not meet eligibility criteria, leaving 67 relevant studies for inclusion (figure 1). Our search strategy identified eligible studies from 20 countries across continental Africa. Nigeria and Tunisia had the highest number of eligible studies (eight studies each), followed by Morocco (seven studies), Algeria, Egypt and South Africa (six studies each), Ghana and Kenya (four studies each) and South Africa (three studies); there were only two studies from Uganda and only one study each from Botswana, Democratic Republic of Congo, Ethiopia, Guinea, Malawi, Mali, Mozambique, Rwanda, Senegal and Sudan (online supplemental table S2). Five studies included data from multiple countries and regions across the continent (East and West Africa, Algeria, Egypt, Ethiopia, Ghana, Morocco, Namibia, Senegal, South Africa and Tunisia). Five studies were translated from French to English and were all based in North Africa. Summary of clinical data can be found in table 1 and online supplemental table S2.

All 67 studies reported TNBC frequency from specific hospital/health facility settings, 34 of which were conducted via academic and academic/university teaching hospitals. Fourteen studies were prospective whereas the others (n=53) were retrospective studies. Additionally, 20 studies included some form of biased sampling (eg, all metastatic cases, tissue microarrays, age cut-offs), whereas the remaining studies included were either random sampling or population-based. Of the included studies, 8 (12%), 37 (55%) and 22 (33%) were classified as low, moderate and high risk of bias, respectively (online supplemental figures S1 and S2, online supplemental tables S3 and S4), after using the risk of bias assessment tool for prevalence studies by Hoy *et al*.[19] Most studies were scored as high risk of bias due to data acquisition (e.g., study population). However, according to criteria set by the Hoy *et al*. risk of bias tool, data were interpreted appropriately for most studies (e.g., having a clear definition of TNBC, appropriate numerator/denominator for frequencies). The eight studies that were low risk of bias were based in Algeria (n=1), Botswana

Table 1 Summary of study variables for included studies across Africa and by region

Study variables	All studies (n=67)	North African studies (n=29)	East African studies (n=10)	Southern African studies (n=8)	Central African study (n=1)	West African studies (n=17)	West and East African studies (n=2)
Mean age (SD)	49.21 (5.25) (n=42)	48.47 (6.35) (n=17)	48.65 (3.34) (n=7)	56.09 (2.53) (n=5)	50.00 (n/a) (n=1)	47.67 (2.65) (n=12)	Not investigated
Median age (IQR)	48.75 (4.50) (n=18)	47.00 (5.72) (n=9)	48.75 (0.87) (n=4)	56.00 (3.00) (n=3)	49.00 (n/a) (n=1)	Not investigated	56.00 (n/a) (n=1)
Grade 1 tumours, median (IQR)	9.56% (7.34) (n=52)	8.44% (6.90) (n=23)	10.66% (9.35) (n=8)	11.40% (1.95) (n=6)	1.15% (n/a) (n=1)	6.06% (11.18) (n=13)	W: 9.56% (n/a), E: 15.25% (n/a) (n=1)
Grade 2 tumours, median (IQR)	51.11% (16.97) (n=53)	57.54% (19.03) (n=23)	44.44% (6.90) (n=8)	46.76% (16.32) (n=7)	51.72% (n/a) (n=1)	51.22% (20.51) (n=13)	W: 33.52% (n/a), E: 30.81%(n/a) (n=1)
Grade 3 tumours, median (IQR)	38.68% (15.04) (n=58)	33.76% (16.40) (n=27)	41.11% (13.92) (n=8)	39.53% (16.90) (n=7)	47.13% (n/a) (n=1)	38.83% (18.89) (n=14)	W: 56.92% (n/a), E: 43.95%(n/a) (n=1)
Positive lymph node status, median (IQR)	64.68% (20.99) (n=42)	58.50% (15.40) (n=23)	70.53% (11.91) (n=6)	64.66% (28.00) (n=3)	Not investigated	91.38% (25.07) (n=10)	Not investigated
Premenopausal, median (IQR)	58.86% (18.16) (n=30)	58.40% (13.87) (n=13)	57.00% (17.19) (n=5)	37.10% (n/a) (n=1)	60.92% (n/a) (n=1)	68.48% (17.26) (n=7)	Not investigated
TNBC frequency, median (IQR)	25.00% (19.41) (n=67)	23.00% (9.02) (n=29)	25.00% (13.08) (n=10)	20.43% (7.32) (n=8)	14.94% (n/a) (n=1)	49.4% (13.60)(n=17)	n/a

*Two studies investigated both West and East African populations in their respective manuscripts.
E, East African participants; n/a, not applicable; W, West African participants.

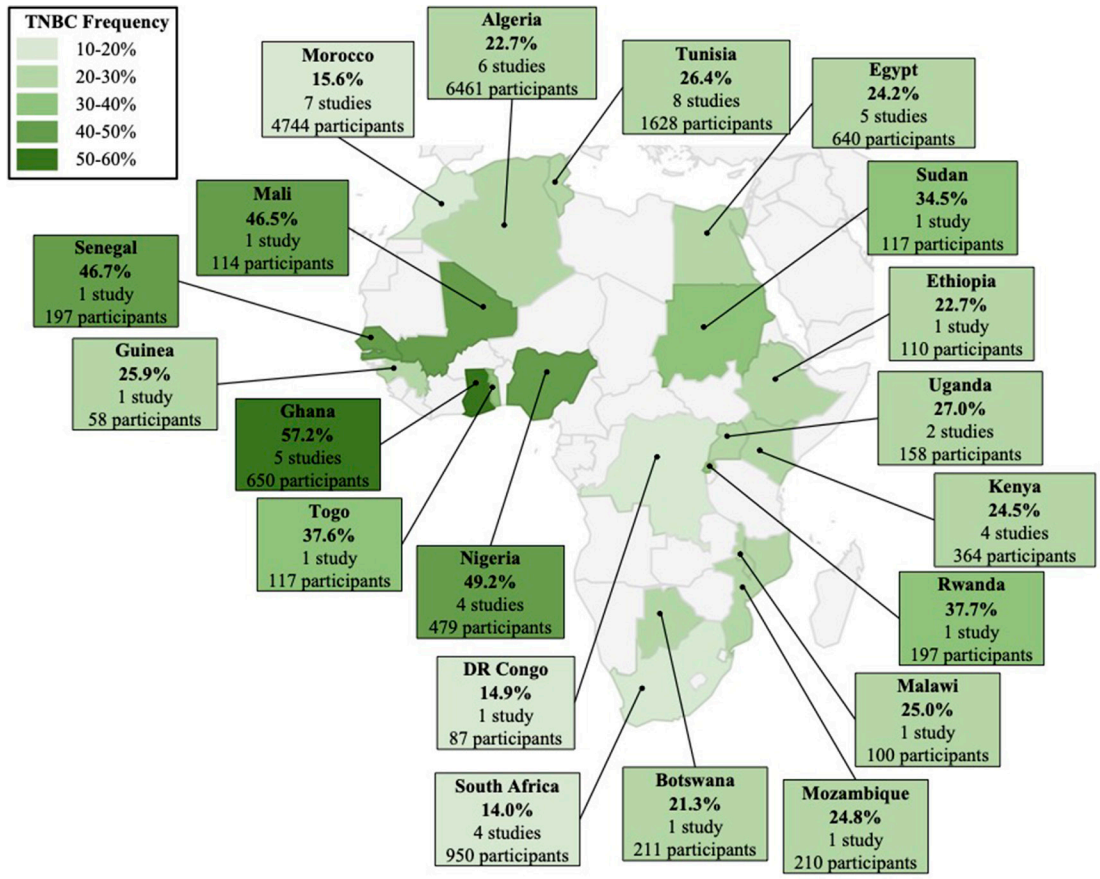

Figure 2 Pooled TNBC frequencies out of all BCa subtypes from studies done across African countries. Data represent pooled TNBC frequencies among all BCa subtypes reported in unique studies done in populations from stated countries. Pooled frequencies were calculated if the country had more than one study as stated within the meta-analysis. Estimates do not account for heterogeneity, IHC cut-offs and size of the respective populations. BCa, breast cancer; IHC, immunohistochemistry; TNBC, triple-negative breast cancer.

(n=1), Malawi (n=1), Rwanda (n=1), South Africa (n=2) or multiple countries (n=2).

After identifying unique study populations per country (n=60, figure 1), TNBC estimates from the meta-analysis, number of studies and participants per country were highlighted (figure 2). Overall TNBC frequency from included studies representing countries across the African continent was estimated to be 27.0%; 95% CI: 24.0% to 30.2%, I^2=94% (online supplemental table S5). Pooled TNBC frequency estimates per country (online supplemental table S5) ranged from 14.0% in South Africa (95% CI: 9.6% to 19.8%, I^2=75%) to 57.2% in Ghana (95% CI: 43.6% to 69.8%, I^2=82%). When investigating estimates per region (figure 3), TNBC frequency was lowest in Central Africa (n=1, 14.1%; 95% CI: 8.9% to 24.1%) and highest in West Africa (n=15, 45.7%; 95% CI: 38.8% to 52.8%, I^2=91%). For these two analyses with pooled estimates per country and per region, heterogeneity (I^2) was estimated at 94%, indicative of high between study variability. When investigating the effect of risk of bias on study estimates, none was observed (online supplemental figure S3). Pooled TNBC estimates were also stratified by use of a validated tool for receptor status testing. Pooled TNBC frequency was higher (n=25, 30.1%; 95% CI: 24.4% to 34.7%, I^2=95%) in studies that reported the use of a validated tool for assessing receptor expression, when compared with studies that did not (n=35, 24.7%; 95% CI: 21.6% to 28.1%, I^2=93%) (online supplemental figure S4). Between-study heterogeneity was high (I^2=94%) and meta-regression showed that these estimates were not statistically significant (online supplemental figure S5A, p=0.057, β coefficient=0.267). When investigating TNBC estimates by the tool used for ER/PR and HER2 cutoffs, pooled TNBC frequency was higher in studies that used the Allred 1998 and Reiner's scale scoring for ER/PR cutoffs and in older versions of American Society of Clinical Oncology(ASCO)/College of American Pathologists(CAP)ASCO/C guidelines when compared with more recent versions for HER2 status (figure 4). There was also an association between publication year and TNBC estimates where meta-regression showed a decrease in effect estimate with increasing publication year (online supplemental figure S5B, p<0.001, β coefficient=−0.075). Influence analyses showed that two studies contributed largely to heterogeneity and influence on overall estimates (online supplemental figure S6). After conducting Egger's test (online supplemental figure S7, p<0.002) and funnel

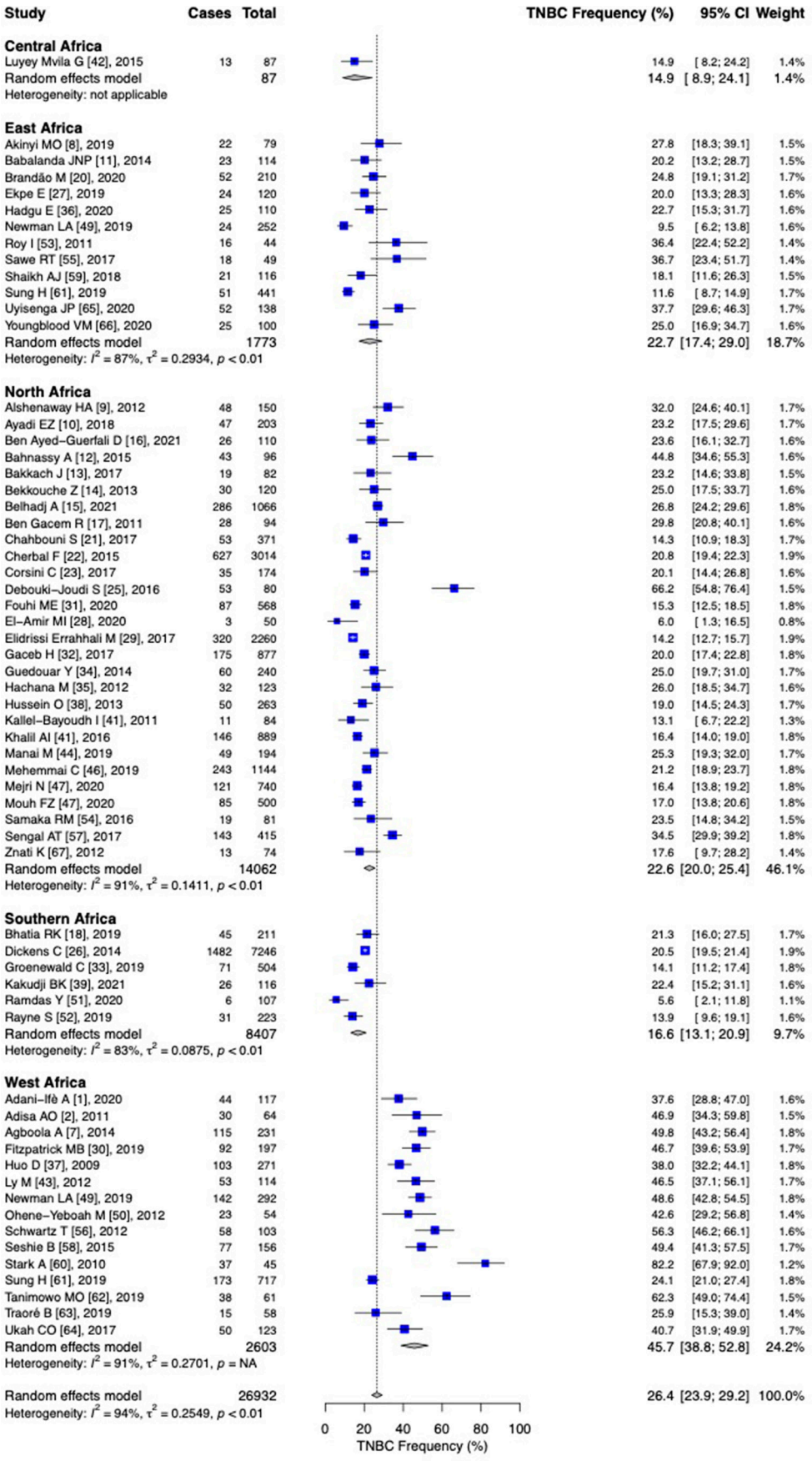

Figure 3 Pooled TNBC frequency in Africa by region. Cases are defined as participants in a study who were identified as triple negative, and total is the number of participants with breast cancer with known receptor status in the study. TNBC, triple-negative breast cancer.

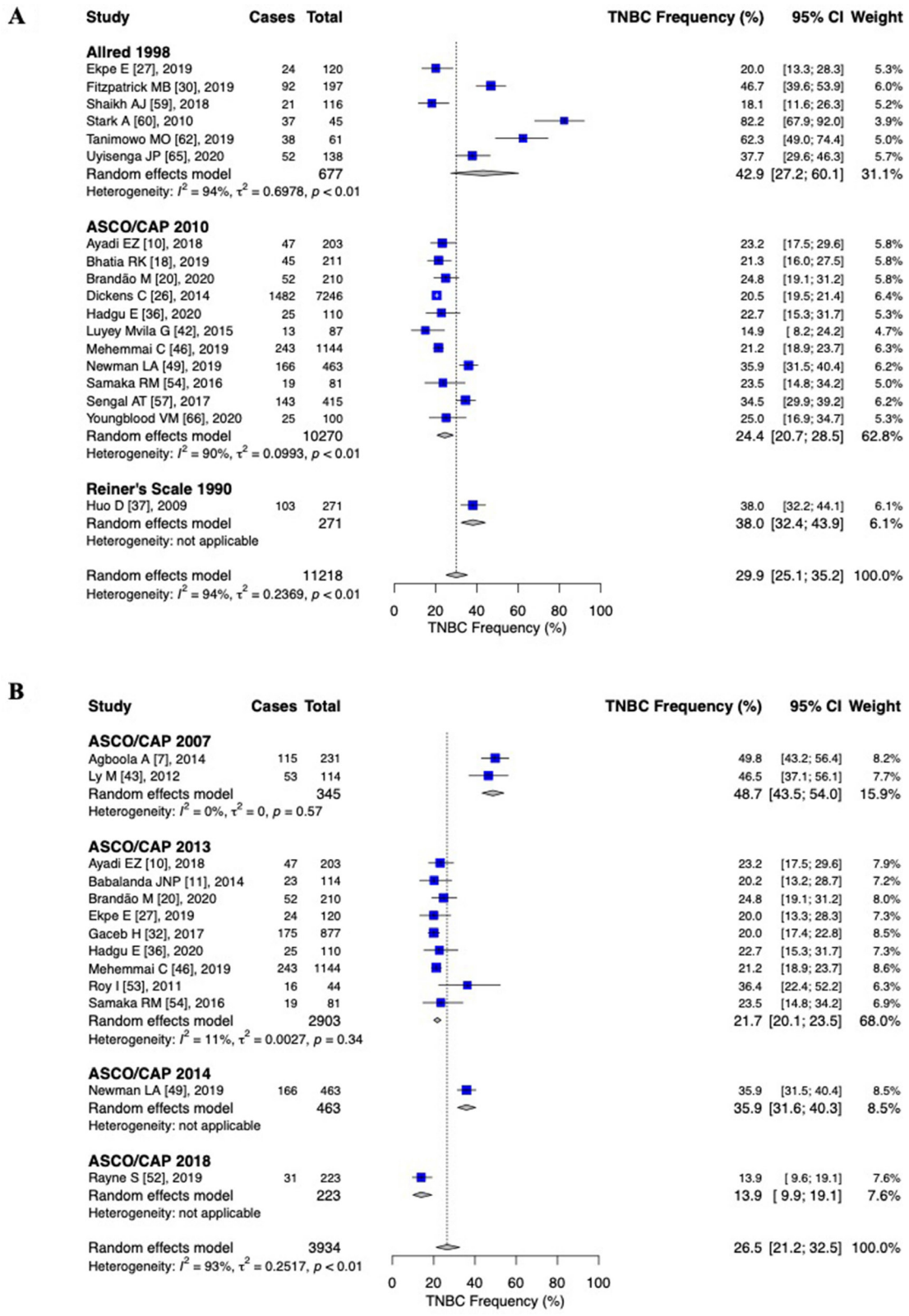

Figure 4 Pooled TNBC frequency in Africa by tool used for (A) ER/PR status and (B) HER2 status. Cases are defined as participants in a study that were identified as triple negative, and total is the number of participants with breast cancer with known receptor status in the study. ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; TNBC, triple-negative breast cancer.

plot analysis (online supplemental figure S8), a significant publication bias was identified.

The overall certainty of evidence for this systematic review and meta-analysis was judged as very low using the GRADE approach. Our judgement was downgraded due to risk of bias, indirectness and publication bias.

DISCUSSION

In this systematic review and meta-analysis of 67 studies on African women with BCa, we found that there was a high frequency of TNBC (27.0%) in cases reported across Africa although this varied depending on country and region. TNBC frequency was highest in West African populations (45.7%) compared with other regions across continental Africa (14.9%–22.7%). This is consistent with increased TNBC/ER-negative prevalence observed in populations with high West African ancestry[15 22 23] in the Caribbean[24 25] and in North America.[26] In an USA population-based study (2010–2014), TNBC prevalence in non-Hispanic white women was estimated to be ~8%, whereas it was ~15% in non-Hispanic Black women.[23] Additionally, TNBC prevalence was estimated to be ~8% and~25% in white and Black women, respectively, in a UK cancer registry-based population in London.[27] These high frequencies of TNBC across Africa and the African diaspora are concerning as triple-negative breast tumours have a greater propensity to metastasize to vital organs such as the brain[28] and are typically more aggressive due to lack of targeted therapies.

When investigating clinical factors, the reported mean and/or median age at diagnosis was under 50 in 35 out of the 47 studies reporting age. Young age at diagnosis (under age 40) has been previously reported to be associated with triple-negative and HER2-positive cancers as well as more aggressive clinical outcome.[29] Indeed, this poor prognosis of patients with TNBC was evident as most of the included studies reported a high percentage of grade 3 tumours, lymph node positivity and TNBC frequency. It must however be noted that a younger age at diagnosis is also routinely observed in lower-income and middle-income countries as this is also reflective of the population structure.[30] Therefore, this observed lower age at diagnosis may be indicative of the population distribution rather than the intrinsic aggressive biology of the tumours. To consider this possibility, we investigated associations with mean and median age at diagnosis and effect estimates and found no association (online supplemental figure S5C, p= 0.209, β coefficient=−0.022; online supplemental figure S5D, p= 0.311, β coefficient=−0.039). More advanced stage tumours and lymph node involvement at presentation may also be attributable to poor infrastructure and lack of BCa awareness and screening. A recent study of BCa across sub-Saharan Africa found that the majority of cases diagnosed were late-stage, emphasising the need for early diagnosis.[31] Two separate studies from Nigeria and Ghana both found that most of the information obtained about BCa was from mass media and there was a general poor knowledge of BCa-associated risk factors.[32 33] The Ghanaian-based study also found that the rate of breast self-examination, and clinical breast examination were higher than that of obtaining mammograms[33] which emphasizes the need to promote screening programmes in a culturally relevant setting. It should be noted however that mammography has been associated with a two times higher chance of detecting ER-positive BCa compared with ER-negative BCa[34] which might be contributing to the relatively higher TNBC frequency observed across West African countries when compared with Southern African countries, where mammography is more accessible.

Many studies were excluded on the account of not assessing ER, PR and HER2 status. With respect to receptor status, 30 out of the 67 studies used validated guidelines (ASCO/CAP,[35–40] Allred[41] or Reiner's Scale[42]) for receptor status cut-offs. Such variability in classifying receptor status (ie, the use of other guidelines with different cut-offs) affects the resulting treatment for patients with a diagnosis and how TNBC frequencies are calculated in each study. After stratifying studies by use of ASCO-CAP guidelines, which account for specimen fixation and cut-offs for ER/PR expression at 1%, there was a decrease in pooled TNBC frequency (24.4%) compared with those that used Allred or Reiner's Scale (cut-off at 10%) resulting in TNBC frequency of 42.9% and 38.0%, respectively (figure 4A). A similar trend was observed for ASCO/CAP guidelines with respect to assessing HER2 status where more recent guidelines correlated with lower TNBC frequency compared with older guidelines (figure 4B). Thus, meta-regression with publication year was done and indeed there was an association with effect estimates (p<0.002, β coefficient=−0.075, online supplemental figure S5B). A similar trend was recently reported for East African-based studies conducted before and after 2013; ER/PR positivity was lower before 2013 compared with after 2013.[43] The variability in how receptor status is assessed highlights a need for increased capacity to conduct immunohistochemical receptor status testing to further enhance BCa diagnoses and classification. It must be noted, however, that IHC might not be feasible for many of the hospitals/health centres across Africa and international collaborations should be encouraged to assist with building such capacity. One Nigerian study noted cost to be a barrier—IHC was performed on only 31% of the reported cases.[44] This study also stated that ASCO/CAP guidelines could not be adhered to for HER2 due to the high cost of fluorescence *in situ* hybridization in the case of an equivocal HER2 score. In contrast, South Africa has an extensive healthcare system with a comprehensive standardized national public health system for routinely assessing BCa receptor status.[45] The disparity in access to diagnostic and therapeutic tools across the continent could also be contributing to the lack of receptor status data and higher BCa burden reported here.

To our knowledge, this is the first systematic review and meta-analysis with an in-depth analysis on TNBC

frequency across continental Africa. However, there are some limitations to be considered. IHC and specimen collection and processing are not equally accessible, and neither are they uniformly done across the African continent. Specimen fixation, storage time of the samples and other preanalytical IHC variables have been previously shown to impact accuracy of IHC results.[46] It was estimated that up to 20% of IHC results globally are inaccurate based off of these preanalytical variables.[47] Furthermore, the true frequency of TNBC is not ascertainable due to lack of population-based data. Our search strategy identified representation from 20 African countries to be included with low representation from Central Africa (n=1) which was similarly observed in a recent systematic review and meta-analysis that investigated BCa incidence across Africa with 22 African countries and low representation from Central Africa (n=2).[5] Another caveat to consider is that there are no validated search strategies for observational studies and thus some studies may be missed. As expected, there was considerable heterogeneity in our meta-analyses. High heterogeneity could be due to the number of studies, or the varying ethnicities across Africa. We graded our confidence in the evidence presented as 'very low' using the GRADE assessment due to high heterogeneity, high risk of bias studies included and low representation across the continent (indirectness); however, given the available data, this is the best estimate of TNBC frequency across the African continent.

This study provides the closest estimate of TNBC frequency across the different regions of continental Africa. Considerations should be made at the country level to address IHC protocols and adherence to ASCO-CAP guidelines wherever possible. There is a clear disparity across the continent (with respect to diagnostic and therapeutic tools) that needs to be effectively addressed to prevent BCa burden. Priority should also be given to implementing culturally relevant BCa awareness programmes as these have been proven to increase cancer awareness knowledge and thus could decrease preventable deaths from BCa.[48] There is also a dearth of knowledge across the continent about BCa subtype prevalence in general. This should be addressed as soon as possible by the establishment of cancer registries before the burden of BCa and other chronic diseases drastically increase with the epidemiological transition that has already started to take place across Africa.

Author affiliations
[1]Biology, McMaster University, Hamilton, Ontario, Canada
[2]African-Caribbean Cancer Consortium, Philadelphia, Pennsylvania, USA
[3]Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada
[4]Osgoode Hall Law School, York University, Toronto, Ontario, Canada
[5]Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada
[6]Terrence Donnelly Centre for Cellular and Biomolecular Research, University of Toronto, Toronto, Ontario, Canada
[7]Institute of Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada
[8]Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[9]McMaster University Library, McMaster University, Hamilton, Ontario, Canada
[10]Department of Oncology, McMaster University, Hamilton, Ontario, Canada
[11]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
[12]Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada
[13]Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada
[14]Biostatistics Unit, Father Sean O'Sullivan Research Centre, St. Joseph's Healthcare, Hamilton, Ontario, Canada
[15]Centre for Development of Best Practices in Health (CDBPH), Yaoundé Central Hospital, Yaoundé, Cameroon
[16]Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University, Cape Town, South Africa
[17]Department of Internal Medicine, Section of Medical Oncology, Yale University Yale Cancer Center, New Haven, Connecticut, USA
[18]Department of Computer Science, Yale School of Engineering and Applied Science, Yale University, New Haven, Connecticut, USA

Twitter Shawn M Hercules @ShawnHercules and Juliet M Daniel @bajanjules27

Acknowledgements The coauthors would like to thank Jessica Garden for reviewing and amending our French to English Google-translated documents.

Contributors SMH was involved in conceptualisation, study design, literature search, data collection, data analysis, data interpretation, cowriting original draft, review and editing. MA, CC and SMM were responsible for literature search, data collection, data analysis, cowriting original draft, review and editing. AS was responsible for conceptualisation, study design, cowriting original draft, review and editing. OP was involved in study design, literature search, review and editing. GP and LM helped in data analysis, data interpretation, review and editing. KRMB was responsible for data interpretation, review and editing. JMD acted as the guarantor and was involved in conceptualisation, study design, data interpretation, supervision, funding acquisition, review and editing.

Funding This study was partially funded by the Natural Sciences and Engineering Research Council of Canada (NSERC; grant number RGPIN-2020-06822), Canadian Breast Cancer Foundation/Canadian Cancer Society Research Institute (CBCF/CCSRI; grant number 316252) and the Canadian Institute for Health Research (CIHR; grant number PJT-173223) for data collection storage and trainee stipends. We have not been paid to write this article by a pharmaceutical company or any other agency.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. All data relevant to the study are included in the article or uploaded as supplementary information and other data are available upon reasonable request.

ORCID iDs
Shawn M Hercules http://orcid.org/0000-0002-1094-094X
Meena Alnajar http://orcid.org/0000-0001-6150-581X
Chen Chen http://orcid.org/0000-0002-6230-3563
Stefan M Mladjenovic http://orcid.org/0000-0003-0446-9300
Bolade Ajarat Shipeolu http://orcid.org/0000-0002-7249-6610
Olga Perkovic http://orcid.org/0000-0003-2324-0691
Lawrence Mbuagbaw http://orcid.org/0000-0001-5855-5461
Kim RM Blenman http://orcid.org/0000-0001-6070-0728
Juliet M Daniel http://orcid.org/0000-0002-3497-0772

REFERENCES

1 Pace LE, Shulman LN. Breast cancer in sub-Saharan Africa: challenges and opportunities to reduce mortality. *Oncologist* 2016;21:739–44.
2 DeSantis CE, Bray F, Ferlay J, *et al*. International variation in female breast cancer incidence and mortality rates. *Cancer Epidemiol Biomarkers Prev* 2015;24:1495–506.
3 International Agency for Research on Cancer. GLOBOCAN 2020. Available: http://globocan.iarc.fr/Default.aspx [Accessed 14 Apr 2021].
4 Huo D, Ikpatt F, Khramtsov A, *et al*. Population differences in breast cancer: survey in Indigenous African women reveals over-representation of triple-negative breast cancer. *J Clin Oncol* 2009;27:4515–21.
5 Adeloye D, Sowunmi OY, Jacobs W, *et al*. Estimating the incidence of breast cancer in Africa: a systematic review and meta-analysis. *J Glob Health* 2018;8:010419.
6 Newman LA, Kaljee LM, Disparities H. Health disparities and triple-negative breast cancer in African American women: a review. *JAMA Surg* 2017;152:485–93.
7 Lukong KE, Ogunbolude Y, Kamdem JP. Breast cancer in Africa: prevalence, treatment options, herbal medicines, and socioeconomic determinants. *Breast Cancer Res Treat* 2017;166:351–65.
8 Prat A, Pineda E, Adamo B, *et al*. Clinical implications of the intrinsic molecular subtypes of breast cancer. *Breast* 2015;24 Suppl (2):S26–35.
9 Bassey-Archibong BI, Hercules SM, Rayner LGA, *et al*. Kaiso is highly expressed in TNBC tissues of women of African ancestry compared to Caucasian women. *Cancer Causes Control* 2017;28:1295–304.
10 Wright N, Rida P, Rakha E, *et al*. Panoptic overview of triple-negative breast cancer in Nigeria: current challenges and promising global initiatives. *J Glob Oncol* 2018;4:1–20.
11 DeSantis CE, Ma J, Gaudet MM, *et al*. Breast cancer statistics, 2019. *CA Cancer J Clin* 2019;69:438–51.
12 Stark A, Kleer CG, Martin I, *et al*. African ancestry and higher prevalence of triple-negative breast cancer: findings from an international study. *Cancer* 2010;116:4926–32.
13 Brewster AM, Chavez-MacGregor M, Brown P. Epidemiology, biology, and treatment of triple-negative breast cancer in women of African ancestry. *Lancet Oncol* 2014;15:e625–34.
14 Eng A, McCormack V, dos-Santos-Silva I. Receptor-defined subtypes of breast cancer in Indigenous populations in Africa: a systematic review and meta-analysis. *PLoS Med* 2014;11:e1001720.
15 Zakharia F, Basu A, Absher D, *et al*. Characterizing the admixed African ancestry of African Americans. *Genome Biol* 2009;10:R141.
16 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264–9.
17 Stroup DF, Berlin JA, Morton SC. *Meta-analysis of observational studies in epidemiology: a proposal for reporting*. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008–12.
18 Krithikadatta J. Normal distribution. *J Conserv Dent* 2014;17:96–7.
19 Hoy D, Brooks P, Woolf A, *et al*. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol* 2012;65:934–9.
20 Balshem H, Helfand M, Schünemann HJ, *et al*. Grade guidelines: 3. rating the quality of evidence. *J Clin Epidemiol* 2011;64:401–6.
21 R Core Team. R: a language and environment for statistical computing. R foundation for statistical computing 2020.
22 Moreno-Estrada A, Gravel S, Zakharia F, *et al*. Reconstructing the population genetic history of the Caribbean. *PLoS Genet* 2013;9:e1003925.
23 Scott LC, Mobley LR, Kuo T-M, *et al*. Update on triple-negative breast cancer disparities for the United States: a population-based study from the United States cancer statistics database, 2010 through 2014. *Cancer* 2019;125:3412–7.
24 Hercules SM, Hercules JC, Ansari A, *et al*. High triple-negative breast cancer prevalence and aggressive prognostic factors in Barbadian women with breast cancer. *Cancer* 2020;126:2217–24.
25 Ragin C, Banydeen R, Zhang C, *et al*. Breast cancer research in the Caribbean: analysis of reports from 1975 to 2017. *J Glob Oncol* 2018;4:1–21.
26 DeSantis CE, Ma J, Goding Sauer A, *et al*. Breast cancer statistics, 2017, racial disparity in mortality by state. *CA Cancer J Clin* 2017;67:439–48.
27 Jack RH, Davies EA, Renshaw C, *et al*. Differences in breast cancer hormone receptor status in ethnic groups: a London population. *Eur J Cancer* 2013;49:696–702.
28 Jin J, Gao Y, Zhang J, *et al*. Incidence, pattern and prognosis of brain metastases in patients with metastatic triple negative breast cancer. *BMC Cancer* 2018;18:446.
29 Gómez-Flores-Ramos L, Álvarez-Gómez RM, Villarreal-Garza C, *et al*. Breast cancer genetics in young women: what do we know? *Mutat Res Rev Mutat Res* 2017;774:33–45.
30 Bidoli E, Virdone S, Hamdi-Cherif M, *et al*. Worldwide age at onset of female breast cancer: a 25-year population-based cancer registry study. *Sci Rep* 2019;9:14111.
31 Jedy-Agba E, McCormack V, Adebamowo C, *et al*. Stage at diagnosis of breast cancer in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Glob Health* 2016;4:e923–35.
32 Azubuike S. Breast cancer risk factors and signs: how much do Nigerian women know? *International Journal of Advanced Medical and Health Research* 2017;4:40–3.
33 Opoku SY, Benwell M, Yarney J. Knowledge, attitudes, beliefs, behaviour and breast cancer screening practices in Ghana, West Africa. *Pan Afr Med J* 2012;11:28.
34 Howlader N, Altekruse SF, Li CI, *et al*. Us incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst* 2014;106. doi:10.1093/jnci/dju055. [Epub ahead of print: 28 Apr 2014].
35 Allison KH, Hammond MEH, Dowsett M, *et al*. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. *J Clin Oncol* 2020;38:1346–66.
36 Wolff AC, Hammond MEH, Allison KH, *et al*. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of clinical Oncology/College of American pathologists clinical practice guideline focused update. *J Clin Oncol* 2018;36:2105–22.
37 Wolff AC, Hammond MEH, Hicks DG, *et al*. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of clinical Oncology/College of American pathologists clinical practice guideline update. *J Clin Oncol* 2013;31:3997–4013.
38 Wolff AC, Hammond MEH, Hicks DG, *et al*. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of clinical Oncology/College of American pathologists clinical practice guideline update. *Arch Pathol Lab Med* 2014;138:241–56.
39 Hammond MEH, Hayes DF, Wolff AC, *et al*. American Society of clinical oncology/college of American pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Oncol Pract* 2010;6:195–7.
40 Wolff AC, Hammond MEH, Schwartz JN, *et al*. American Society of clinical Oncology/College of American pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol* 2007;25:118–45.
41 Allred DC, Harvey JM, Berardo M, *et al*. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. *Mod Pathol* 1998;11:155–68.
42 Reiner A, Neumeister B, Spona J, *et al*. Immunocytochemical localization of estrogen and progesterone receptor and prognosis in human primary breast cancer. *Cancer Res* 1990;50:7057–61.
43 Popli P, Gutterman EM, Omene C, *et al*. Receptor-Defined breast cancer in five East African countries and its implications for treatment: systematic review and meta-analysis. *JCO Glob Oncol* 2021;7:289–301.
44 Ukah CO*et al*. The immunohistochemical profile of breast cancer in Indigenous women of Southeast Nigeria.
45 Cubasch H, Dickens C, Joffe M, *et al*. Breast cancer survival in Soweto, Johannesburg, South Africa: a receptor-defined cohort of women diagnosed from 2009 to 11. *Cancer Epidemiol* 2018;52:120–7.
46 Gown AM. Diagnostic immunohistochemistry: what can go wrong and how to prevent it. *Arch Pathol Lab Med* 2016;140:893–8.

47 Agrawal L, Engel KB, Greytak SR, *et al*. Understanding preanalytical variables and their effects on clinical biomarkers of oncology and immunotherapy. *Semin Cancer Biol* 2018;52:26–38.

48 Jemal A, Brawley OW. Increasing cancer awareness and prevention in Africa. *Ecancermedicalscience* 2019;13:939.